

Marfan Syndrome

Long-Term Outcome in Patients With Marfan Syndrome: Is Aortic Dissection the Only Cause of Sudden Death?

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OBJECTIVES	We sought to assess outcomes in a series of young patients with Marfan syndrome and to define the prevalence of ventricular arrhythmias in this patient population.
BACKGROUND	While sudden death is a well-recognized outcome in Marfan syndrome, ventricular arrhythmias are not well described.
METHODS	Patients were followed with echocardiography, electrocardiography, and ambulatory electrocardiography. The prevalence and associated factors for ventricular dysrhythmias were defined.
RESULTS	Seventy patients with Marfan syndrome diagnosed at birth to 52 years were followed for a period of up to 24 years. All patients had cardiovascular involvement and were started on medical therapy. No patient died from aortic dissection, while 4% died from arrhythmias. Ventricular arrhythmias were present in 21% and were associated with increased left ventricular size, mitral valve prolapse, and abnormalities of repolarization.
CONCLUSIONS	Cardiac complications are rare in young patients with Marfan syndrome receiving medical therapy and close clinical follow-up. Sudden death still occurs, and appears more common in patients with a dilated left ventricle. Left ventricular dilation may predispose to alterations of repolarization and fatal ventricular arrhythmias. (J Am Coll Cardiol 2003;41:329–32) © 2003 by the American College of Cardiology Foundation

Sudden death in Marfan syndrome is commonly due to aortic dissection (1). Treatment with beta-blockers is thought to reduce the risk of progressive aortic dilation and sudden death (2,3). While it has been theorized that the structural fibrillin defect (4) may affect the myocardium with a secondary alteration in electrical properties (5), arrhythmias have not been well recognized as a cause of morbidity and mortality (5). We sought to evaluate a large cohort of patients with Marfan syndrome followed at a single institution to assess long-term outcome, with particular emphasis on causes of sudden death. In addition, we sought to define the prevalence of ventricular dysrhythmias and abnormalities of repolarization, and to determine clinical variables associated with ventricular ectopy.

METHODS

Patient population. All consecutive patients with Marfan syndrome followed in a subspecialty cardiology clinic of a single institution were identified. The diagnosis of Marfan syndrome was made in accordance with the revised diagnostic criteria (6). Clinical data including age at diagnosis, duration of follow-up, presence of family history of sudden

death associated with Marfan syndrome, medications, previous cardiac surgery, and clinical status were obtained.

Echocardiography. All patients underwent semi-annual echocardiograms. Data obtained from the echocardiogram at last visit or prior to death was used for data analysis. Aortic root dimension, obtained from the parasternal long axis view (7), was expressed as an absolute value, and as a value normalized for body surface area. Previously reported normal aortic values were used (8). Aortic root dilation was defined as being present if the dimension was >2 standard deviations above predicted. The left ventricular end-diastolic dimension (LVED) was expressed as an absolute value, and as a Z-score based on normative data previously reported (9,10). The presence of mitral valve prolapse (MVP) and the degree of mitral regurgitation (MR) or aortic insufficiency were noted.

Electrocardiography. Routine electrocardiogram (ECG) was performed on initial evaluation of all patients before starting medical therapy, and repeated yearly. Initial and most recent ECGs were reviewed, and QTc and QTu intervals were calculated when a U-wave $>50\%$ of the height of the T-wave was present.

24-h ambulatory ECG monitoring. Patients had an initial 24-h ambulatory ECG monitor placed while off of medication for assessment of ventricular arrhythmias. All subsequent monitoring, in those patients who had multiple recordings, was while on medication. Ventricular ectopy was defined as being present if there were >10 premature

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Abbreviations and Acronyms

ECG	= electrocardiogram
LV	= left ventricle
LVED	= left ventricular end-diastolic dimension
MR	= mitral regurgitation
MVP	= mitral valve prolapse

ventricular contractions per h (11). Ventricular couplets and runs of ventricular tachycardia were documented.

Data analysis. Data are expressed as frequencies, means \pm standard deviations, or medians with ranges where appropriate. Patients were divided into two groups based on the presence or absence of ventricular ectopy. Patient characteristics and test results for the two groups were compared using Fischer exact test and chi squared analysis for categorical variables, and *t* tests and Kruskal Wallis analysis of variance for continuous variables. Survival from birth, and from time of diagnosis, for the two groups was plotted using Kaplan-Meier estimates and compared using the log rank test. Independent factors associated with the presence of ventricular ectopy, as specified in the preceding text, were sought in multiple logistic regression analysis.

RESULTS

Patient population. Seventy patients (34 male and 36 female) with Marfan syndrome were identified, with a median age at diagnosis of 10 years (range, birth to 52 years). Sixty-three patients (90%) were diagnosed and followed from childhood (<18 years). Median age at follow-up was 17 years (range, 1.5 to 55 years) with a median follow-up duration of 6 years (range, 20.2 months to 24.5 years). A family history of Marfan syndrome was present in 24 of the 49 families (49%), with a positive family history of sudden death associated with Marfan syndrome present in 13 families (27%). All patients were started on antihypertensive drug therapy for prophylaxis against aortic root dilation, but only 58 patients (83%) were maintained on therapy because of the presence of adverse effects. Twenty-six patients (37%) were maintained on a beta-blocker, 25 patients (36%) on an angiotensin-converting enzyme inhibitor, 2 patients (3%) on a calcium-channel antagonist, and 5 patients (7%) on a combination of the above agents. The choice of medication was determined by evolving patient practice.

Six patients (8%) underwent aortic surgery: five requiring nonemergent aortic root replacement and one requiring emergency aortic graft placement to repair a ruptured descending thoracic aortic aneurysm evident on presentation. No patient required mitral valve surgery.

There were three patient deaths occurring at 11, 21, and 23 years of age. All were sudden, with no evidence of aortic dissection or other structural causes of death, evident at autopsy. All deaths were deemed arrhythmogenic.

Table 1. Cardiac Characteristics

Characteristic	Prevalence
Aortic root dilation	63 (90%)
Mitral valve prolapse	34 (49%)
Mitral insufficiency	15 (21%)
Mild	13
Moderate	2
Severe	0
Left ventricular dilation	34 (68%)
Aortic insufficiency	6 (8%)
Mild	4
Moderate	2
Severe	0
Left ventricular systolic dysfunction	8 (11%)
QTc prolongation	11 (16%)
QTu prolongation	37 (60%)
Ventricular ectopy	13/62 (21%)
Ventricular tachycardia	4/62 (6%)

Cardiac characteristics. Table 1 demonstrates the cardiovascular findings. All patients had cardiovascular involvement identified during follow-up, with 63 patients (90%) having aortic root dilation with a mean aortic dimension of 34 ± 8 mm ($129 \pm 23\%$ predicted). Left ventricular dilation, as defined by a Z-score exceeding +2, was present in 34 patients (68%). Mean percent predicted LVED was $112 \pm 15\%$, with a mean Z-score of 2.2 ± 1.7 . Eight patients (11%) had evidence of reduced left ventricular (LV) function, with a shortening fraction <30%.

Electrocardiographic characteristics. All patients underwent ECG at presentation and during routine follow-up. All patients were found to be in sinus rhythm. Eleven patients (16%) had QTc prolongation >440 ms on initial and subsequent ECG. Thirty-seven patients (60%) had prominent U waves and evidence of a prolonged QTu with a mean of 622 ± 57 ms.

24-h ambulatory ECG monitoring. Routine 24-h ambulatory ECG monitoring has become part of our standard practice for assessment of patients with Marfan syndrome, and was performed in 62 patients. Ventricular ectopy (>10 premature ventricular contractions/h or ventricular couplets or ventricular tachycardia) was noted to be present in 13 patients (21%), of whom 4 patients (6%) also had nonsustained ventricular tachycardia. No patient was noted to have sustained ventricular ectopy (ventricular tachycardia >30 s). The percent of ventricular ectopic beats ranged from 1% to 24%.

Factors associated with ventricular ectopy. Table 2 summarizes the clinical characteristics. Patients with ventricular ectopy had a greater prevalence of MVP with associated MR and LV dilation. These patients had a higher prevalence of repolarization abnormalities, with a greater QTc and QTu interval.

All three deaths occurred in the patients with ventricular ectopy, with Kaplan-Meier estimates for survival from birth for both groups shown in Figure 1. When assessing survival from time of diagnosis, ventricular ectopy remained a significant predictor ($p = 0.036$).

Table 2. Factors Associated with Ventricular Ectopy

Variable	Ventricular Ectopy Present	Ventricular Ectopy Absent	p Value
Mean LVED Z score	4.0 ± 1.6	1.6 ± 1.5	< 0.001
Mean % predicted aortic root size	140 ± 25	127 ± 22	0.06
MVP	13/13 (100%)	21/49 (43%)	< 0.001
Mitral insufficiency	8/13 (62%)	7/49 (14%)	< 0.001
Aortic insufficiency	3/13 (23%)	3/49 (6%)	0.1
QTc (ms)	437 ± 33	410 ± 25	0.003
QTu prolongation	652 ± 44 (n = 12)	604 ± 62 (n = 22)	0.03
Any medical therapy	11/13 (84%)	42/49 (85%)	1
Beta blocker therapy	10/13 (76%)	19/49 (39%)	0.03
Family history of sudden death	8/13 (62%)	15/49 (35%)	0.08
Median age at diagnosis in years (range)	10.2 (3–39)	10 (0–51)	0.69

LVED = left ventricular end diastolic dimension; MVP = mitral valve prolapse.

Multiple logistic regression analysis showed only increased LVED Z-score (odds ratio 2.27 per 1 standard deviation increase in Z-score; 95% confidence interval, 1.44 to 3.59; $p < 0.001$) to be an independent factor associated with ventricular ectopy. After controlling for this variable, the other variables were not independently associated with the presence of ventricular ectopy, although many of the variables were highly correlated, particularly with LVED Z-score. As such, we sought to determine other factors that were significantly associated with LVED Z-score in the total study population. Higher LVED Z-score was significantly associated with a higher percent predicted aortic root dimension (Pearson correlation $r = 0.34$; $p = 0.005$), longer corrected QT interval ($r = 0.50$; $p < 0.001$), and longer corrected QTu interval ($r = 0.39$; $p = 0.02$). A higher LVED Z-score was noted in patients with a family history of sudden death (mean 2.85 vs. 1.81 in those without; $p = 0.02$). Significant independent factors associated with higher LVED Z-score noted in general linear regression modeling included longer QTc interval on initial ECG and the presence of aortic insufficiency.

Four patients had nonsustained ventricular tachycardia on ambulatory ECG monitoring. Of these patients, two died

suddenly despite medical therapy with beta blockade, one remains alive on amiodarone with arrhythmia control, and one patient, desiring no other treatment, remains alive on beta-blocker therapy alone with persistence of symptomatic nonsustained ventricular tachycardia.

Table 3 summarizes the clinical features of the nonsurvivors. Two patients had stable aortic root dimensions and the third had undergone previous aortic root replacement. All nonsurvivors had ventricular couplets or ventricular tachycardia on routine 24-h ECG assessment.

DISCUSSION

We report on the long-term outcome of a large series of young patients with Marfan syndrome. Patients were followed semi-annually and started on medical management early in the course of their disease. Over an extended period of follow-up, few patients required surgical intervention, however, the incidence of ventricular arrhythmias was significant with a mortality rate from presumed arrhythmogenic death of 4%, exceeding the rate of aortic rupture.

Left ventricular dilation has been associated with abnormalities of repolarization and arrhythmogenic death in adults with congestive heart failure (12). Even in the absence of regurgitant lesions, LV dilation occurs commonly in patients with Marfan syndrome and is associated with altered repolarization that may subsequently lead to ventricular arrhythmias. Patients with Marfan syndrome have been documented to have increased aortic wall stiffness (13) that may lead to increased LV afterload and associated LV dilation. The arrhythmias noted in our patient population may have occurred secondary to alterations in repolarization seen in the dilated left heart.

Previous medical therapies have focused on reducing the progression of aortic root dilation as a means to improving survival (2,3). Beta-blocker therapy has been routinely used (2,3). Beta-blockers have been the mainstay of treatment for repolarization abnormalities seen in other diseases, including the long QT syndrome (14), raising the question of whether patients with Marfan syndrome may receive additional benefit from such therapy. Angiotensin-converting

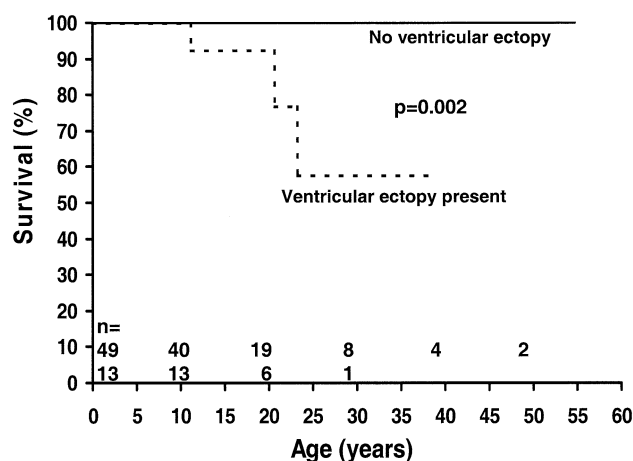


Figure 1. Kaplan-Meier estimates of survival from birth stratified by the presence or absence of ventricular ectopy in patients who had 24-h ambulatory electrocardiogram assessment.

Table 3. Characteristics of Nonsurvivors

Fam Hx SD	Age at Dx (yrs)	Meds	Age at Death	%SF	LVED Z score	LVED (mm)	MVP	MR	AI	% Predicted Aortic Root	QTc (ms)
+	10	BB	23	35	5.5	59	+	moderate	—	158%	517
—	10	BB	11	33	5.1	63	+	None	—	130%	426
—	7	BB	21	25	3.7	58	+	Mild	—	176%	450

AI = aortic insufficiency; BB = beta blocker; Dx = diagnosis; Fam Hx SD = family history of sudden death; LVED = left ventricular end diastolic dimension at time of Holter; Meds = medications; MR = mitral insufficiency; MVP = mitral valve prolapse; %SF = percent shortening fraction

enzyme inhibitors have been associated with reduced QT dispersion, reduced LV size, and improved survival (12) in adults with congestive heart failure. Their role in Marfan syndrome remains unknown. Given the association of angiotensin-converting enzyme inhibitors with reduction in ventricular size and reduction in MR, one might suspect a beneficial role of such therapy in this patient group as LV size and MR were both associated with increased ventricular ectopy.

Study limitations. Within this study, patients were on a variety of medical therapies with no discernible benefit of any one therapy. While we noted a higher prevalence of ventricular ectopy in patients on beta-blocker therapy, this may be confounded by the fact that ventricular ectopy was an indication for such therapy. No inferences regarding the impact of medical therapies on the incidence of ventricular arrhythmias can be drawn from this study data alone. Ventricular ectopy, as defined herein, has previously been reported to be rare (0% to 6%) amongst healthy controls (15), but was not reassessed in this study. Ventricular ectopy is common in adults with isolated MVP (16) and has been found to be highly correlated with abnormalities of repolarization. Mitral valve prolapse may have contributed to the increased frequency of ventricular arrhythmias noted in our study population. As the number of patient deaths in this study were few, it is difficult to fully gauge the clinical impact of ventricular arrhythmias in Marfan patients. Ongoing study of the causes of sudden death in Marfan patients is required. We chose to assess impact of ventricular ectopy on survival from the time of birth rather than from the time of diagnosis as Marfan syndrome is a congenital condition. It is possible that some patients died without a diagnosis of Marfan syndrome being made which would alter the survival curve.

CONCLUSIONS

In summary, we have documented a high prevalence of LV dilation with associated abnormalities of repolarization in a large series of children and adults with Marfan syndrome. Such repolarization abnormalities are associated with an increased risk of ventricular ectopy and possibly sudden death. Routine 24-h ECG monitoring is critical to the ongoing assessment of these patients. Close follow-up of patients, even in the presence of a stable aortic root dimension, is required. Patients with Marfan syndrome and ventricular dysrhythmias may be at particularly high risk for sudden death. Aggressive treatment modalities including

amiodarone or internal defibrillators may be warranted in select patients. Further research into the effects of routinely employed anti-hypertensives on ventricular performance, repolarization and the incidence of ventricular ectopy, in this patient group is suggested.

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